

## **REMARKS**

### **Status of the Specification**

This paper amends the specification to correct various references to trademarks and to correct paragraph numbering. Applicant notes that the prior amendments to the specification of December 17, 2003 are taken into account in the substitute specification submitted herewith. Applicant also notes that prior amendments of May 1, 2007, September 4, 2007 and April 30, 2008 were not entered because they were alleged to be non-compliant (in Office Actions of July 31, 2007, November 30, 2007, and March 3, 2009, respectively). Applicant has included a markup and a clean copy for the Examiner's convenience. No new matter is added by these amendments to the specification.

### **Status of the Claims**

This paper adds claims 51 and 52, amends claims 1, 4, 6, 8, 12, 30 and 31 and cancels claims 36, 39-45 and 47-48. Accordingly, after amendment, claims 1, 4-18, 30-32, 46, 49-52 are pending and under examination, and claims 49 and 50 are pending but withdrawn. No new matter is added in these claim amendments.

Support for the claim amendments is found in the canceled claims and generally throughout the specification and in the Examples. Support for new claims 51 and 52 can be found, at least, at paragraph 0080, Examples 3 and 4. Support for amendment of claim 1 is also found, at least, in paragraphs 0019 and 0078. Support for amendment of claim 4 is also found, at least, in paragraph 0036. Applicants respectfully remind the Examiner that the withdrawn and partially withdrawn claims are eligible for rejoinder upon allowability of the genus claim.

### **Claim Interpretation**

Applicants submit that, as previously presented, the claims accurately recited that amplification using primers comprising SEQ ID NOs:1-4 requires their use in a single reaction. The rejection states: "Particularly, it is noted that the claims as written do not in fact require, e.g.

that all 4 primers be employed in a single tube or other container when performing the “amplifying” step of the claims; rather, the claims merely require “amplifying... from a sample” using the primers.” Office Action at p. 10. The claim as previously drafted requires the use of multiplex amplification primers. In contrast to the Examiner’s position, Applicants submit that *by definition*, a multiplex reaction is performed in a single reaction.<sup>1</sup> Although Applicants believe that their interpretation of the phrase “multiplex amplification primers” is correct, for the sole purpose of advancing prosecution Applicants have amended the claim to recite that the amplification is performed in a single reaction.

Applicants submit that because the Examiner hinged her obviousness rejection over the prior art based on the interpretation that the claim did not require amplification performed in a single reaction and the amendment now does so explicitly, the claims are now distinguished over the cited prior art. Accordingly, the rejection under 35 U.S.C. §103 should be withdrawn. Applicants provide a more formal argument below.

#### **Rejections Under 35 U.S.C. §112, second paragraph**

Claims 1, 4-18, 30-32, and 46 stand rejected for indefiniteness for reciting limitations enumerated as “steps,” all of which the Examiner alleges lack antecedent basis. Applicants respectfully traverse and assert that the recitation of “steps” in the rejected claims clearly identify the enumerated method steps of the preceding claims even though the steps are identified by letter designation only (i.e., without the word “step”). However, in order to expedite prosecution, Applicants have amended claims to delete the word “step” and make other grammatical changes, as appropriate. These amendments thereby render the rejections moot and the rejections should be withdrawn.

Claims 1, 4-18, 30-32, and 46 stand rejected for indefiniteness for reciting a method for identifying at least one polymorphism in the preamble, but dependent claims 8 and 12-17

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<sup>1</sup> For example, multiplex amplification is the amplification of two or more target sequences in the same reaction. <http://www.everythingbio.com/gloss/definition.php?word=Multiplex+Amplification>

reference “said... polymorphism” while other dependent claims (9, 10) reference “at least one of ...polymorphisms.” Applicants respectfully traverse. Applicants have amended claims 8 and 12 to recite “at least one” to moot the rejection. Accordingly, the rejections should be withdrawn.

Claim 18 stands rejected for indefiniteness because it is allegedly unclear how the claim further limits claim 1. Applicants submit that because claim 1 is directed to a method of identifying the presence or absence of at least one cytochrome P450 2D6 polymorphism in a sample, claim 18 reciting the method of claim 1, further comprising detection of wildtype P450 2D6, further limits claim 1 to the instance where *all* polymorphisms are identified as absent. Consequently, claim 18 is a subset of the potential outcomes recited in claim 1. Accordingly, the rejections should be withdrawn.

### **Rejections Under 35 U.S.C. §103**

Claims 1, 4, 6-9, 11-18, 30-32, and 46 stand rejected as obvious over Anastasio et al. (WO 02/38589; “Anastasio”), in view of Stuvén et al. (Pharmacogenetics (1996) 6:417-421; “Stuvén”) and Steen et al. (Pharmacogenetics (1995) 5:215-223; “Steen”), as evidenced by Goelet et al. (WO 92/15712; “Goelet”). The Examiner alleges that Anastasio describes various cytochrome P450 2D6 (“CYP2D6”) polymorphisms and methods for genotyping and haplotyping the same. The Examiner acknowledges that Anastasio does not specifically disclose Applicants’ claimed method for determining CYP2D6 genotype, but notes that Anastasio instructs that the polymerase-mediated primer extension methods of Goelet may be used. The Examiner looks to Stuvén et al. for alleged disclosure of SEQ ID NOs: 1 and 2, to Steen et al. for alleged disclosure of SEQ ID NOs: 3 and 4, and alleges that the claimed invention does not include an amplifying step in a single reaction. Applicants respectfully traverse this rejection.

Amended claim 1 encompasses methods for detecting the presence or absence of CYP2D6 polymorphisms (i.e., determining CYP2D6 genotype) by (i) amplifying a CYP2D6 gene sequence using amplification primers of SEQ ID NOs: 1-4 in a single reaction, and (ii) performing a primer extension reaction using a plurality of extension primers that specifically

bind to the CYP2D6 gene sequence which, when extended by one nucleotide, are indicative of the presence or absence of a polymorphism. Detection of the polymorphisms in the primer extension reaction is facilitated by the use of distinctively labeled ddNTPs in the primer extension reaction.

The method of claim 1 (and its dependent claims) differs significantly from those disclosed by Anastasio and/or Goelet, and neither Stuvem nor Steen remedy their deficiencies. In particular, none of the cited references teach or suggest performing a multiplex amplification using primers comprising SEQ ID NOs:1-4 in a single reaction followed by multiplex primer extension, as required by the claims.

As an initial matter, Anastasio does not suggest performing a single reaction (i.e., multiplex) amplification reaction to amplify the CYP2D6 gene regions encompassed by the primers of SEQ ID NOs: 1-4. The Examiner alleges that, at page 23, Anastasio suggests investigating multiple polymorphic sites simultaneously. Office Action at page 8. However, a careful reading of the relevant passage in Anastasio reveals that Anastasio suggests “simultaneously amplifying multiple regions of the [CYP2D6 gene] using sets of allele-specific primers...” Anastasio et al. at p. 23, ¶ 3. This is an entirely different amplification and detection strategy from that specified in the rejected claims. The primers of SEQ ID NOs: 1-4 amplify two different regions of the CYP2D6 gene, from which any number of mutations may be assessed (i.e., SEQ ID NOs: 1-4 are not allele-specific). In contrast, the use of allele-specific primers, as suggested by Anastasio, require the *a priori* selection of the mutations to be assessed and do not amplify a target sequence for later assessment.

Goelet does not remedy the deficiency of Anastasio. The Examiner relies on Goelet merely for a demonstration that certain types of primer extension reactions were known in the art. This does not motivate the artisan to perform a multiplex amplification reaction of two distinct regions of the CYP2D6 gene, let alone do so using the amplification primers of SEQ ID NOs: 1-4, specifically.

Finally, neither Stuvén et al. nor Steen et al. motivate the skilled artisan to perform the multiplex amplification of the rejected claims. Instead, each of these secondary references amplifies only single CYP2D6 gene regions individually and provide no motivation for multiplexing. In fact, Stuvén et al. discourages the skilled artisan from multiplexing. Stuvén et al. state:

The 4.7 kb fragment serves as a template for a multiplex allele-specific PCR assay to simultaneously identify the five PM-associated alleles, CYP2D6\*3 (A), \*4 (B), \*6 (T), \*7 (E), AND \*8 (G). Together with the CYP2D6 deletion allele CYP2D6\*5 (D), which can be detected in a separate PCR assay, these alleles are responsible for the PM phenotype in approximately 99% of Caucasian individuals.

Stuvén et al. at p. 417, Abstract (emphasis added).

Applicants point out that the CYP2D6\*5 deletion allele is the same deletion allele assessed by Steen et al., the other secondary reference cited by the Examiner. This teaching by Stuvén et al. illustrates that they were aware of both the multiplexing technique and the CYP2D6\*5 deletion mutation, but discouraged their simultaneous amplification in a single reaction. Therefore, contrary to the Examiner's allegation, not even Stuvén et al. were motivated to combine their amplification reaction with that of Steen et al., much less the skilled artisan aware of both. As a result, the rejection fails to make a *prima facie* case for nonobviousness because the cited prior art fails to teach every element of the rejected claims (i.e., multiplex amplification using SEQ ID NOs: 1-4) and objectively fails to motivate the artisan to modify the prior art methods in the manner alleged by the Examiner.

The remaining pending but rejected dependent claims incorporate all of the limitations of the independent claims and are, therefore, also novel. These rejections are traversed and should be withdrawn.

#### Claims 5

Claim 5 stands rejected as obvious over the above references, in further view of Dovichi et al. (Methods Mol. Biol. 167: 225-239, 2001). The Examiner applies Anastasio et al. in light of Stuvén et al. and Steen et al., as evidenced by Goelet et al. as described above, and notes that none of the reference teach the use of capillary electrophoresis. The Examiner alleges that the teachings of Dovichi et al., when combined with the other references render obvious the rejected claims. Applicants respectfully traverse this rejection.

Dovichi et al. does not remedy the deficiencies of the above references (i.e., does not teach a multiplex amplification using the primers of SEQ ID NOs: 1-4), nor is it asserted by the Examiner for that purpose. Consequently, Dovichi et al. in light of the other cited references does not make obvious claim 5. Accordingly, this rejection should be withdrawn.

#### Claims 10

Claim 10 stands rejected as obvious over Anastasio et al. in view of Stuvén et al. and Steen et al. and as evidenced by Goelet et al., in further view of Pastinen et al. (PCR Applications; Innis, M.A. et al., eds., Academic Press, San Diego, 1999, pp. 521-535). The Examiner applies the combination of Anastasio et al. and other references as discussed above, and notes that Pastinen et al. discloses detecting the CYP2D6\*4 allele by primer extension using a primer comprising SEQ ID NO: 9. Applicants respectfully traverse this rejection.

Pastinen et al. does not teach or suggest performing multiplex amplification prior to the primer extension reaction, let alone a multiplex amplification using Applicants' claimed primers. Thus, Pastinen et al. does not remedy the deficiencies of the basic combination of Anastasio et al. and the other references. nor is it asserted by the Examiner for that purpose. Consequently, Pastinen et al. in light of the other cited references does not make obvious claim 10. Accordingly, this rejection should be withdrawn.

Claim 19 is canceled herewith, rendering the remainder of this rejection moot. Accordingly, this rejection is traversed and should be withdrawn.

**CONCLUSION**

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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